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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED OFFICE (DO/US)

<u>PCT/SE00/02263</u>	<u>16 November 2000</u>	<u>22 November 1999</u>
International Application Number	International Filing Date	Priority Date(s) Claimed

NEW FUNCTIONALIZED POLYMERIC REAGENTS

Title of Invention

PAGE, Patrick

Applicant(s) for DO/US

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- I. Accompanying this transmittal letter are certain items which are required under 35 U.S.C. 371 in order that United States National processing of the above identified International application may commence:
- (X) at the expiration of the applicable time limit under PCT Articles 22 and 39(1) according to the provisions of 35 U.S.C. 371(b).
- () as soon as possible upon receipt of this express request under 35 U.S.C. 371(f).

09/762320-02263

1. The U.S. National fee [35 U.S.C. 371(c)(1)]

a. () was previously transmitted by applicant on (date)_____.

b. (X) is submitted herewith as follows:

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			<u>RATE</u>	<u>FEE</u>	<u>or</u>	<u>RATE</u>	<u>FEE</u>	
Basic Fee	(USPTO NOT ISA OR IPEA)		////	\$500	<u>or</u>	////	\$1000	
Total Claims	-20 =	--	x 9 =		<u>or</u>	x18 =	\$	
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i. (X) Enclosed is a check in the amount of \$1270.

ii. () **Please charge the filing fee, multiple dependent claim fee (if applicable), excess independent claims fee (if applicable), and excess total claims fee (if applicable) to Deposit Account No. 23-1703.**

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2. A copy of the International application as filed [35 U.S.C. 371(c)(2)]:

a. (X) is transmitted herewith.

b. () is not required as the application was filed with the United States Receiving Office.

c. () has been transmitted

- i. ☐ by the International Bureau. Date of mailing of the application (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed.
- ii. ☐ by applicant on (date) _____.
3. A translation of the International application into the English language [35 U.S.C. 371(c)(2)]:
- a. ☐ is transmitted herewith.
- b. ☒ is not required as the application was filed in English.
- c. ☐ was previously transmitted by applicant on (date) _____.
4. Amendments to the claims of the International application under PCT Article 19 [35 U.S.C. 371(c)(3)]:
- a. ☐ are transmitted herewith.
- b. ☐ have been transmitted
- i. ☐ by the International Bureau. Date of mailing of the amendments (from form PCT/IB/308): _____.
- ii. ☐ by applicant on (date) _____.
- c. ☒ have not been transmitted as
- i. ☐ no notification has been received that the International Searching Authority has received the Search Copy.
- ii. ☐ the Search Copy was received by the International Searching Authority but the Search Report has not yet issued. Date of receipt of Search Copy (from form PCT/ISA/202): _____.
- iii. ☐ applicant chose not to make amendments under PCT Article 19. Date of mailing of Search Report (from form PCT/ISA/210): _____.

- iv. (X) the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.
5. A Translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)]:
- a. () is transmitted herewith.
 - b. () is not required as the amendments were made in the English language.
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6. An executed declaration for patent application of the inventor [35 U.S.C. 371(c)(4)] complying with 35 U.S.C. 115:
- a. () was previously submitted by applicant on (date)

 - b. (X) is submitted herewith;
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 - i. (X) is attached to the application.
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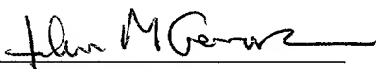
II. Concerning other documents:

1. An International Search Report or Declaration under PCT Article 17(2)(a):
- a. () has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed
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- d. ☐ has been submitted by applicant on (date) _____.
2. A Statement of prior art under 37 CFR 1.97 and 1.98:
- a. ☐ is transmitted herewith including copies of the references cited on the attached form PTO-1449.
- b. ☐ will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).
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3. (X) An executed Assignment is transmitted herewith for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
- a. ☐ **Please charge the \$40.00 assignment recordation fee to Deposit Account No. 23-1703.**
- b. (X) Enclosed is a check in the amount of **\$40**.
4. **Other document(s) or information included:**
- Copy of PCT/RO/101 - The PCT Request Form; and
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Respectfully submitted,

6 February 2001
DATE


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Enclosures

NEW FUNCTIONALIZED POLYMERIC REAGENTS

TECHNICAL FIELD

The present invention relates to polymer supports useful in solution and solid-phase synthesis. It relates more specifically to functionalized polymeric reagents, comprising an acid labile isonitrile moiety. In further aspects the present invention also relates to use of such functionalized polymeric reagents in solution and solid-phase synthesis, a method for preparing an organic compound by solution or solid-phase synthesis using such functionalized polymeric reagents, a method for preparing such functionalized polymeric reagents and to kits comprising the functionalized polymeric reagents according to the invention. The present invention also relates to new intermediates for use in the preparation of the novel functionalized polymeric reagents.

BACKGROUND ART

The use of solid-phase synthesis for the synthesis of organic compounds has received a lot of attention lately. The reason for this is that solid-phase synthesis has several advantages compared to traditional solution-phase synthesis. Examples of such advantages include the ease with which products can be separated and purified from excess reagents by a simple washing step and the rapid isolation of product when cleaved and washed from the polymeric support.

The concomitant evolution of combinatorial chemistry and the improvement in automated syntheses has put a bonus on functionalized polymeric reagent. Combinatorial chemistry, combined with High Throughput Screening has revolutionized the speed with which the pharmaceutical industry can produce and screen compounds.

A prerequisite for solid-phase synthesis is a functionalized and stable polymeric support. Many of the commercially available polymeric supports have been developed for solid-

phase peptide synthesis and are therefore not inevitably suitable for solid-phase synthesis of compounds with non-peptidic structures.

Although highly successful, solid-phase synthesis exhibits several shortcomings due to the nature of heterogeneous reaction conditions, of which non-linear kinetic behavior is one. By replacing insoluble polymers, such as cross-linked polystyrene, with soluble polymers, such as PEG, the familiar reaction conditions of classical organic chemistry is reinstated, and yet product purification is still facilitated through application of macromolecular properties. This methodology in essence avoids the difficulties of solid-phase synthesis while preserving its positive aspects.

A key step in the synthesis of libraries of non-peptidic structures, or other biological active compounds in general, is to find the shortest synthetic pathway in order to speed up the chemistry optimization and production phase. One alternative is to use multicomponent reactions involving at least 3 reactants, which directly gives the product in a very efficient process. Several multicomponent reactions (MCR) have been described in the literature and one of the most widely utilized is the Ugi MCR. Multicomponent reactions can be performed either in solution or on solid phase. Although the solution phase alternative has proven its efficiency for the synthesis of a large number of biological compound, its major drawback is the need of purification steps in order to remove the excess of starting materials. This slows down the overall production process and/or limits its appropriateness for automated or semi-automated synthesis.

One commercially available functionalized polymeric reagent comprising an isonitrile moiety is shown below in Figure 1. The isonitrile moiety can not be cleaved from the polymeric support by acid treatment.

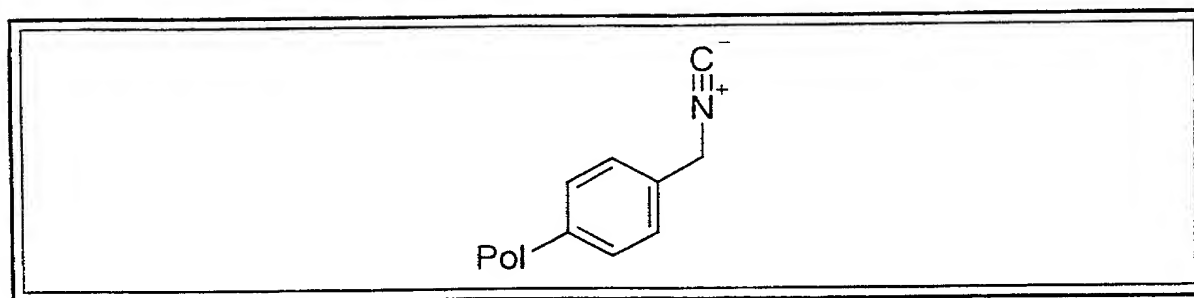


Figure 1. Commercially available functionalized polymeric reagent containing an isonitrile moiety

5 This drawback is overcome by the present invention, which thereby introduces a novel use for functionalized polymeric reagents comprising an isonitrile moiety. Isonitriles have always been a poor source of diversity in combinatorial chemistry. This is due to the low number of commercially available isonitriles and the cost associated with time-consuming efforts of custom syntheses of a large number of diverse isonitriles. The present invention
10 overcomes these problems by use of a resin capture strategy where the reactive isonitrile moiety is attached to the polymeric support in such a way as to make it cleavable by acid. The resin capture strategy used has a further advantage in that it gives no by-products that are fragments of the desired final product. Compounds synthesized by this resin capture strategy and released by acid cleavage are pure and do not require any further purification
15 steps.

SUMMARY OF THE INVENTION

The present invention provides a functionalized polymeric reagent comprising a linker moiety for use in solution and solid-phase synthesis. The linker is compatible with a
20 number of reagents and reaction conditions used in the synthesis of organic compounds. The functionalized polymeric reagent is also useful in combinatorial chemistry.

Thus, one aspect of the present invention is a functionalized polymeric reagent for use in solution and solid-phase synthesis. The functionalized polymeric reagent comprises a

linker, and said linker comprises an acid labile isonitrile moiety. The linker is covalently attached to the polymeric support.

In another aspect the present invention provides a method for preparing an organic compound by solution or solid-phase synthesis. The method comprises the step of immobilizing a substrate compound on the polymeric support via said isonitrile moiety. The thereby attached substrate compound is thereafter taken through at least one further organic reaction step to produce the desired compound, which is thereafter cleaved from the polymeric support and isolated. In a preferred embodiment, said method is performed with a variegated population of substrates and/or a plurality of organic reactions to provide a library of organic compounds.

In another aspect the present invention provides a method for preparing an organic compound by solution or solid-phase synthesis. The method comprises the step of a multi-component reaction being performed on the acid labile isonitril moiety of the functionalized polymeric reagent. In a preferred embodiment the multi-component reaction is an Ugi or an Ugi-type reaction.

In another aspect the present invention provides a method for preparing a functionalized polymeric reagent. The method comprises the step of reacting a suitable polymeric support comprising an amino group with a "formylating" reagent. The thereby produced formamido group is thereafter converted to an isonitrile moiety. In a preferred embodiment the amino group is treated with 2,4,5-trichlorophenylformate in DMF and the resulting formamido group is treated with triphenylphosphine / carbon tetrachloride and triethylamine in dichloromethane.

In another aspect the present invention provides new intermediates for use in the preparation of the novel functionalized polymeric reagents.

Accordingly, it is an object of the present invention to provide a functionalized polymeric reagent for use in solution or solid-phase synthesis.

It is another object of the present invention to provide a method for preparing an organic
5 compound by solution or solid-phase synthesis.

It is another object of the present invention to provide a method for preparing a library of organic compounds.

10 It is another object of the present invention to provide a method for preparing a functionalized polymeric reagent.

It is another object of the present invention to provide a new intermediate for use in the preparation of a functionalized polymeric reagent.

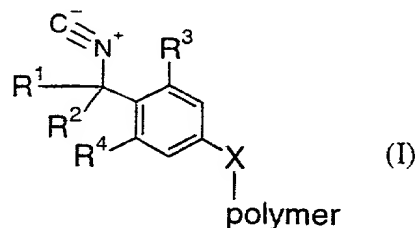
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DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to functionalized polymeric reagents suitable for solution and solid-phase synthesis, to preparation of said functionalized polymeric reagents, and to use
20 of said functionalized polymeric reagents in solution and solid-phase synthesis of organic compounds, including libraries.

In one aspect, the present invention provides a functionalized polymeric reagent for use in solution and solid-phase synthesis. The functionalized polymeric reagent comprises a
25 polymeric support and an acid labile isonitrile moiety, wherein said polymeric support comprises a polymer and a linker. The linker is covalently attached to the polymer and the isonitrile moiety is covalently attached to the linker.

Preferred functionalized polymeric reagents of the present invention are those of Formula I



wherein

X is oxygen, a PEG-chain or a $-(CH_2)_n-CONH-$ group,

5 R^1 is carbon, hydrogen, phenyl, or substituted phenyl group,

R^2 is hydrogen, phenyl, or substituted phenyl group

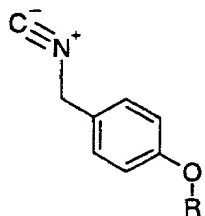
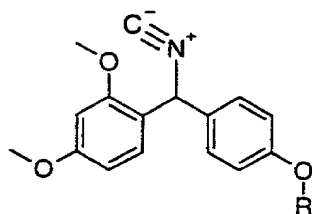
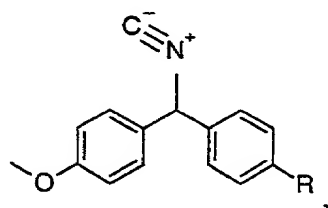
R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

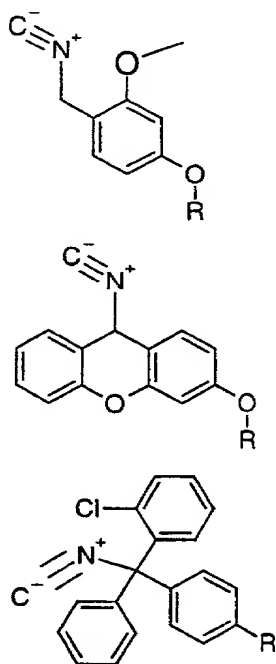
n is an integer from 1 to 4.

10

More preferred functionalized polymeric reagents of the present invention are



15



wherein R is a polymer directly attached to the linker or through a PEG-chain or a –
 5 (CH₂)_n-CONH- group.

The following definitions shall apply throughout the specification and the appended
 claims:

10 The term "functionalized polymeric reagent" denotes a reagent that is covalently attached
 to a linker moiety, and said linker is covalently attached to a polymer.

The term "polymeric support" denotes a polymer covalently attached to a linker moiety,
 which can optionally further be attached to a substrate compound.

The term "linker" denotes a reactive functional group that can be used to link molecules
 15 onto polymeric supports.

The term "acid labile isonitrile" denotes an isonitrile moiety which is cleaved from the
 linker when treated with aqueous trifluoroacetic acid (95%) at room temperature with a
 half time of less than 30 minutes.

The term "substrate compound" denotes a compound to be modified in a subsequent
 20 reaction step.

The term "immobilize" denotes the act of linking, *e.g.* a substrate compound, by means of chemical or biological procedure to a polymeric support.

The term "multicomponent reaction" denotes a one-pot reaction that form products from at least three different starting materials and incorporate substantial portions of these reagents into the product. This includes reactions involving at least three different functional groups, some of which may be parts of the same reagent molecule.

The term "variegated population" denotes a population including at least two different chemical entities, *e.g.*, of different chemical structure. For example, a "variegated population" of nucleophiles would comprise at least two different nucleophiles.

The term "substituted phenyl" denotes a phenyl group substituted with at least one of the following; C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, or phenoxy group.

The term "formylating reagent" denotes a reagent that can convert an amino group into a formamido group.

Polymeric supports

The choice of the soluble or insoluble polymer of the polymeric support is not crucial. Suitable soluble and insoluble polymers therefore consists of those known to the skilled artisan in the art of solution or solid-phase synthesis. Examples of suitable insoluble polymer include, but is not limited to, inorganic substrates, *e.g.* kieselguhr, silica gel and controlled pore glass, and polymeric organic substrates, *e.g.* polystyrene, polypropylene, polyethylene glycol, , as well as composite inorganic/polymeric substrates such as polyacrylamide supported within a matrix of kieselguhr particles. Preferred insoluble polymers are 1% DVB polystyrene and polystyrene-PEG.

Examples of suitable soluble polymers include, but is not limited to, polystyrene (not cross-linked, polyvinyl alcohol, polyethylene imine, polyacrylic acid, polymethylene oxide, PEG, polypropylene oxide, cellulose, polyacrylamide, PEG with 3,5-diisocyanatobenzyl chloride. PEG with 3-nitro-3-azapentane 1,5-diisocyanate, polyvinyl

alcohol-poly(1-vinyl-2-pyrrolidinone, polystyrene-poly(vinyl-substituted monosaccharides), poly(N-isopropylacrylamide)-poly(acrylic acid derivatives).

By replacing insoluble polymers with soluble polymers the familiar reaction conditions of classical organic chemistry is reinstated, and yet product purification is still facilitated through application of macromolecular properties. The present invention thereby avoids the difficulties of solid-phase synthesis while preserving its positive aspects.

Linkers

The choice of the linker is not limited to MAMP resin (amino-(4-methoxyphenyl)methyl polystyrene) (A), and therefore also includes, but is not limited to, Rink amide (B), Wang amino (C), Sasrin amino (D), Sieber amide (E) and 2-chlorotrityl linker (F) shown in Figure 2 below.

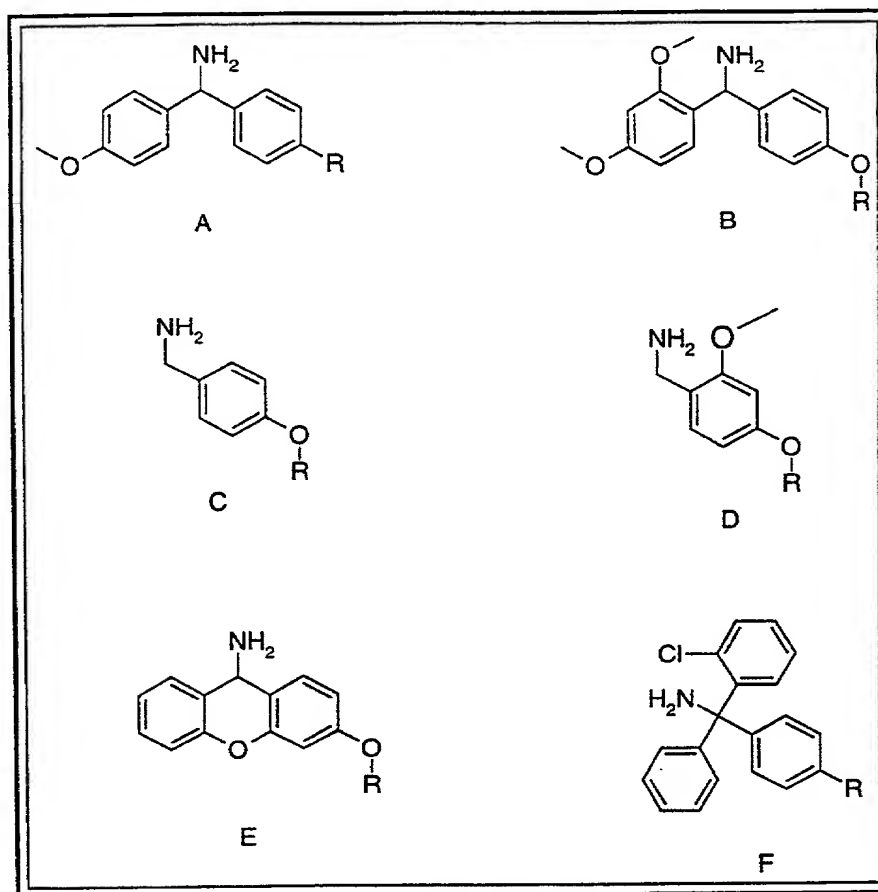


Figure 2. Linkers

In figure 2, R represents the polymeric support either directly attached to the linker or
 5 through a spacer moiety, such as a PEG-chain or a $-(CH_2)_n-CONH-$ group.

Preparation of Functionalized Polymeric Reagents

A simple synthesis of a functionalized polymeric reagent is schematically shown in Figure
 10 3 and described in more detail in Example 1.

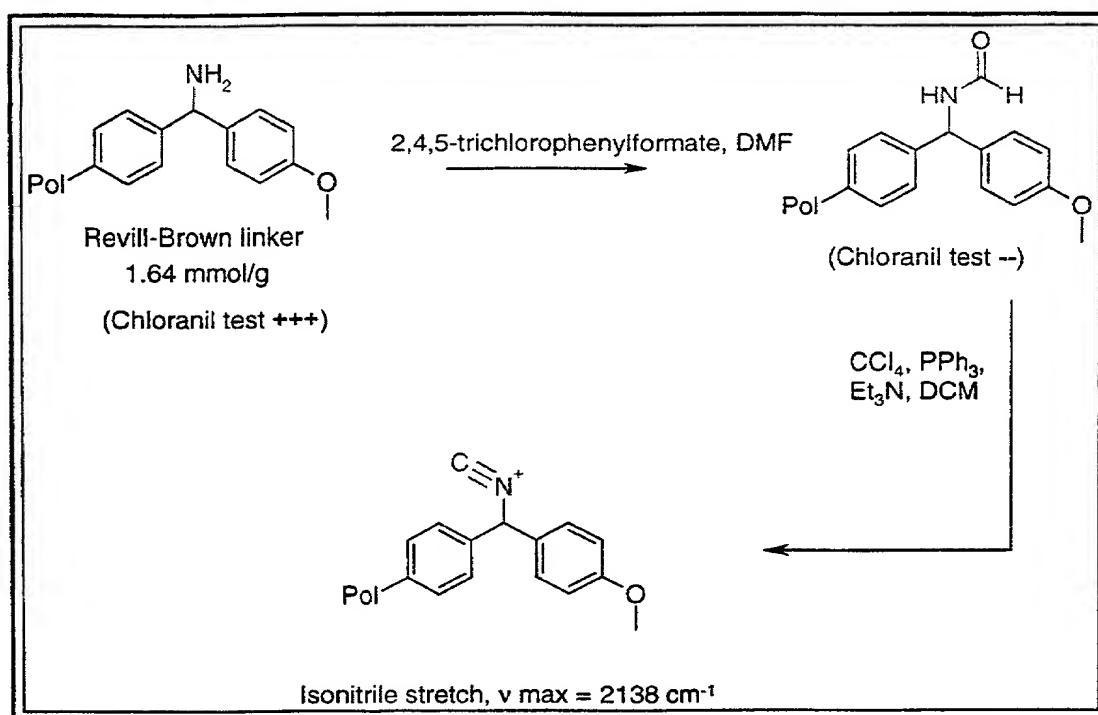


Figure 3. Synthesis of a Functionalized Polymeric Reagent

In this example, the functionalized resin is prepared by mixing a polymeric support (for example, amino MAMP linker 100-200 mesh or 200-400 mesh, commercially available from Novabiochem) in a polar solvent (*e.g.*, DMF) with a suitable "formylating" reagent, *e.g.* 2,4,5-trichlorophenylformate, as shown in figure 3. The reaction can be performed at room temperature or, in certain embodiments, at elevated temperature to ensure completeness of reaction and/or to decrease reaction times. The time required for the reaction can range from about 3 hours to 24 hours or more; an exemplary reaction time is 12 hours at room temperature.

The formed formamido intermediate is thereafter reacted at room temperature with carbon tetrachloride (CCl₄) / triphenylphosphine (PPh₃) in a non-polar solvent, *e.g.*

dichloromethane (DCM) for approximately 3 hours in the presence of a base, *e.g.* triethylamine (Et₃N) to give the corresponding isonitrile.

This procedure has the advantage that it requires only a minimum number of synthetic steps, uses readily available reagents, and provides a functionalized polymeric reagent in good yield with simple purification steps.

- 5 Completeness of reaction with the functionalized polymeric reagent or polymeric support can be assessed according to standard techniques such as microanalysis, spectroscopic analysis, or by colorimetric tests. For example, the formation of an isonitril moiety can be monitored by Fourier-transform infra-red spectroscopy (FT-IR), e.g., by monitoring the isonitril stretch at 2138 cm^{-1} . Once the reaction has reached a pre-selected
- 10 endpoint, the resin is preferably purified by washing. To ensure removal of excess reagents, several cycles of washing, preferably with solvents of a variety of polarities, can be carried out.

- Once the functionalized polymeric reagent or polymeric support has been prepared and
- 15 washed it is stable at room temperature for long periods of time. The functionalized polymeric reagent can be stored for extended periods of time without loss of activity.

Cleavage of Compounds from the Polymeric Support

- 20 It will be appreciated from the foregoing that the present invention provides a functionalized polymeric reagent, comprising an acid labile isonitrile moiety for use in solution and solid-phase synthesis. Compounds can be cleaved from the polymeric support with a variety of acids including, but not limited, to the following; TFA in DCM (20%), 4 M HCl in dioxane, HF, acetic acid in DCM (80%). A person skilled in the art can easily
- 25 optimize the conditions to get the best possible result in the cleavage step. In general, the resin-bound compounds are preswollen in DCM for 10 min, the resin filtered and a solution of DCM:TFA:water (80:18:2) or 4M HCl in Dioxane was added and the reaction mixture was agitated for 1 hour at room temperature. The solution is filtered and evaporated to give the crude final compound.

Synthesis of Organic Compounds on the Polymeric Support

The present invention provides a method for synthesizing organic compounds by solution or solid-phase synthesis. In one embodiment, the method includes the steps of immobilizing a substrate compound on a polymeric support and at a later stage, cleaving the product from the polymeric support with an acid. As described in more detail below, in certain embodiments, the substrate compound is provided as a variegated population of substrate compounds, such that a library of organic compounds can be prepared.

Persons skilled in the art will appreciate that the immobilized substrate compound can be chemically manipulated while attached to the polymeric support. Thus, in certain embodiments, the method for synthesizing organic compounds by solution or solid-phase synthesis can include a plurality of further reaction steps, after the immobilizing step but before the cleaving step. Such synthetic manipulations include reactions, which are standard in solution and solid-phase synthesis. The reaction conditions for such manipulations will generally be selected to avoid cleavage of the substrate compound from the support, unless such concomitant cleavage is desired.

Combinatorial Chemistry on the Polymeric Support

Functionalized polymeric reagents of the present invention are suitable for use in combinatorial chemistry. Accordingly, in another aspect, the invention provides a method for the solution or solid-phase supported chemical synthesis of libraries. In one embodiment, the method comprises the step of reacting a substrate compound, which is immobilized on a polymeric support of the invention, with reagent molecules under conditions such that a library of compounds is prepared. In this embodiment, at least one of the substrate compound or the reagent molecule is provided as a variegated population thereof. It will be appreciated that the method can include the step of cleaving the library

of compounds from the polymeric support. Such a cleavage step can be concomitant with the reacting step, or, in certain embodiments, can be a separate cleavage step.

Combinatorial libraries can be screened to determine whether any members of the library have a desired activity, and, if so, to identify the active compounds. Soluble compound libraries can be screened by affinity chromatography with an appropriate receptor to isolate ligands for the receptor, followed by identification of the isolated ligands by conventional techniques (e.g., mass spectrometry, NMR, and the like). Contacting the compounds with a soluble receptor can screen immobilized compounds; preferably, the soluble receptor is conjugated to a label (e.g., fluorophores, calorimetric enzymes, radioisotopes, luminescent compounds, and the like) that can be detected to indicate ligand binding. Alternatively, immobilized compounds can be selectively released and allowed to diffuse through a membrane to interact with a receptor.

Combinatorial libraries of compounds can also be synthesized with "tags" to encode the identity of each member of the library. In general, this method features the use of inert, but readily detectable, tags that are attached to the solid support or to the compounds. When an active compound is detected (e.g., by one of the techniques described above), the identity of the compound is determined by identification of the unique accompanying tag. This tagging method permits the synthesis of large libraries of compounds that can be identified at very low levels.

A variegated population of substrate compounds can provide diversity in a combinatorial synthesis. Several methodologies have been developed to perform combinatorial chemistry. Examples of such methodologies include, but is not limited to, the mix and split technology and IRORI MiniKans.

Multicomponent Reactions on the Polymeric Support

The polymeric support of the invention is suitable for use with multicomponent reactions, but not limited to them. Multicomponent reactions have become increasingly common and have been extensively reviewed see e.g. Lutz Weber, *Synlett* 1999, no 3, 366-374; Kevin Short, *Tetrahedron* vol. 53, no 19, 6653-6679, 1997; Sang Kim, *Tetrahedron Letters*, 39 (1998) 6993-6996; Blackburn, *Tetrahedron Letters* (1998) 39, 5469-5472. Bienayme, *Angew. Chem. Int. Ed.* (1998) 37, no 16; Blackburn 39, (1998) 3635-3638 *Tetrahedron Letters*.

In a multicomponent reaction three or more component molecules can react simultaneously or close to simultaneously with each other to provide a molecule which has incorporated substantial portions of these reagent molecule without any isolation of intermediates. This includes reactions involving at least three different functional groups, some of which may be parts of the same reagent molecule. In general a multicomponent reaction is sequences of bimolecular reaction steps that proceed according to the zipper principle, i.e. each reaction step is a prerequisite for the following step. Examples of multicomponent reactions include but are not limited to, α -aminoalkylation (Mannich), Passerini, Ugi and Ugi-type. Ugi and Ugi-type reactions are preferred multicomponent reactions to be used with the polymeric supports of the present invention. Ugi and Ugi-type reactions give access to compounds and functionalities of great interest for a medicinal chemist, e.g. heterocyclic compounds.

Accordingly, in another aspect, the invention provides methods for the multicomponent synthesis of organic compounds. In one embodiment, the method comprises the step of reacting the isonitrile moiety with at least two reagent molecules simultaneously under conditions such that a multicomponent reaction is achieved.

A preferred embodiment of the present invention is schematically shown below in Figure 4.

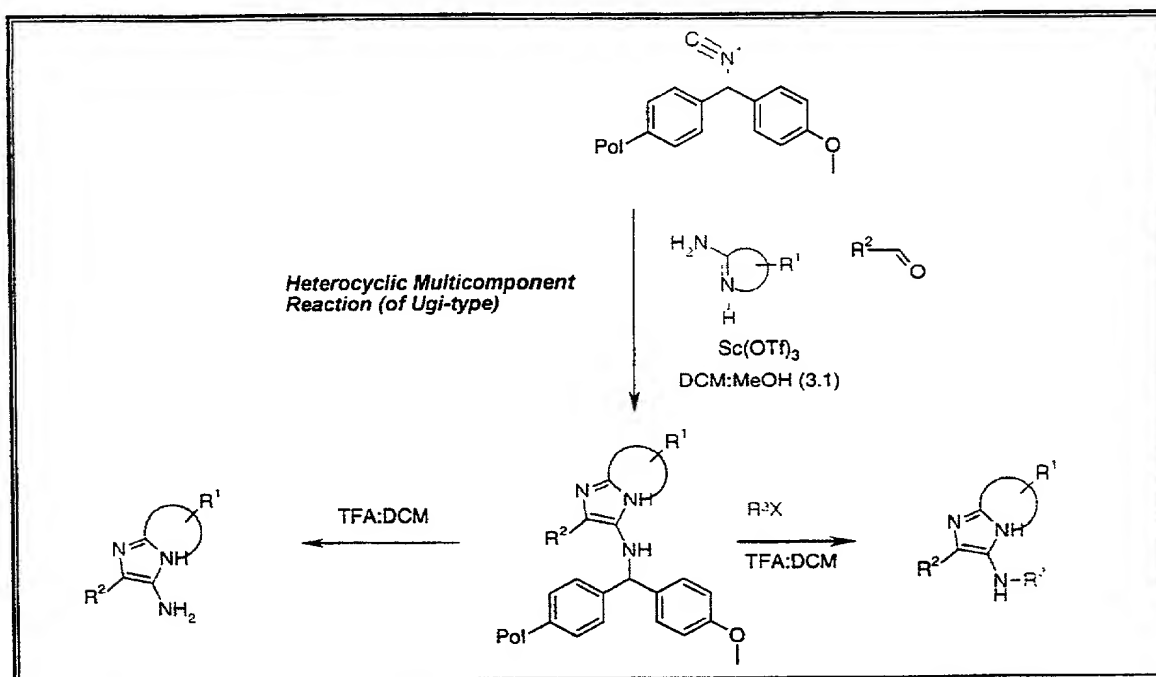


Figure 4. Heterocyclic Multicomponent Reaction

The preferred embodiment shown in Figure 4 is advantageous since it allows a
 5 multicomponent reaction to be performed directly onto the acid labile isonitrile moiety of the functionalized polymeric reagent.

The example outlined above consists of a multicomponent Ugi-type condensation wherein the isonitrile moiety of the functionalized polymeric reagent is reacted with 2 different
 10 source of diversity, aldehydes and heteroaromatic amidines. This Ugi-type reaction leads efficiently and in a one step process to the fused 3-aminoimidazoles, using the resin capture strategy. The final compounds are of high purity after acid cleavage.

3-aminoimidazoles has been synthesized according to the present invention. A wide range
 15 of aldehydes and heteroaromatic amidines was utilised to test the functionalized polymeric reagent and showed the efficiency of the resin capture by obtaining a high yield and excellent purity of the final products. Typical procedure for the synthesis of fused 3-aminoimidazoles by Ugi type reaction and resin capture strategy is described in Example 3, below.

The fused 3-aminoimidazoles contains a nitrogen atom, involved in an amine bond with the polymeric support, which can be further reacted with various electrophilic molecules, *e.g.* acyl halides, alkyl halides, or sulfonyl halides, and thereafter, be cleaved from the polymeric support. This tandem reaction process (MCR + acylation/alkylation) increases the diversity which can be introduced onto the 3-fused aminoimidazole core. The thereby introduced additional diversity is a further advantage of the present invention, since the access of these compounds by traditional solution-phase without polymeric support is cumbersome, since the corresponding isonitriles are either not commercially available or time-consuming to synthesize. Due to the low number of commercially available isonitriles able to be utilised in combinatorial chemistry (<20) and the cost and time-consumption of custom syntheses, the isonitriles have always been the poorest source of diversity involves in the Ugi reaction.

One of the advantages of the present invention is to overcome this kind of problem. The amino functionality of the aminoimidazoles can be utilised for further reactions, such as acylation or alkylation reactions. For example, acyl chlorides, sulfonyl chlorides or alkyl halides can be used as source of diversity and will enhance the diversity of the aminoimidazoles. The Tandem reaction concept by coupling a multi component reaction with an additional alkylation or acylation step makes the whole process highly efficient with respect to the final diversity of the aminoimidazoles synthesized. The present invention also have a positive impact on the size and the speed by which a library can be generated. The tandem 3CC+1 strategy has enhanced the diversity of the fused 3-aminoimidazoles by using 3 non-exhaustive sources of diversity, *i.e.* acyl chlorides, alkyl halides and sulfonyl chlorides. The typical procedures for the synthesis of these compounds are described below in Example 3.

The polymeric support of the present invention can also be used in general organic chemistry manipulations, such as cycloaddition reactions, as a dehydrating agent or as a

scavenger, *e.g.* for the removal of alkyl halides, phosphines, acid chlorides, aldehydes and ketones.

Kits

5

The present invention also provides a kit for use in solution and solid-phase synthesis. The kit includes a functionalized polymeric reagent of the present invention, *i.e.* for use in solution and solid phase chemistry, preferably in a container or package.

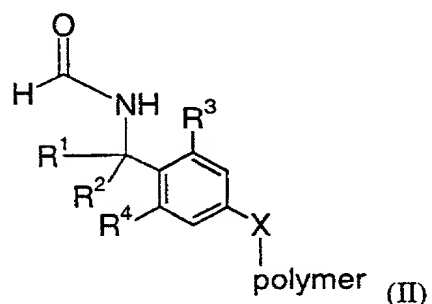
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Intermediates

It is an object of the present invention to provide new intermediates for use in the preparation of the novel functionalized polymeric reagents.

15

Useful intermediates according to the present invention are compounds of Formula II



wherein

X is carbon, oxygen, a PEG-chain, or a $-(CH_2)_n-CONH-$ group

20 R^1 is hydrogen, phenyl, or substituted phenyl group,

R^2 is hydrogen, phenyl, or substituted phenyl group,

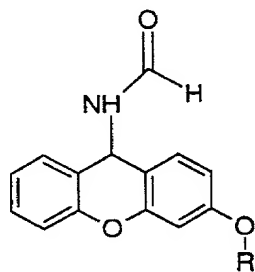
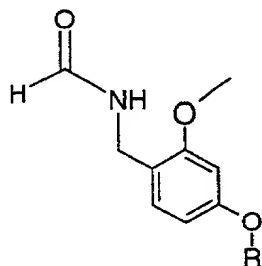
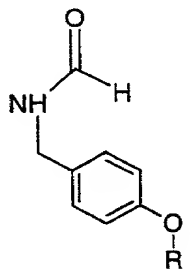
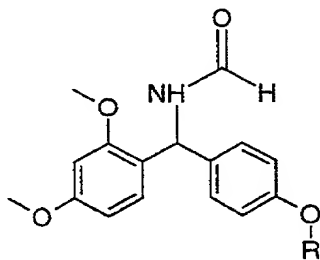
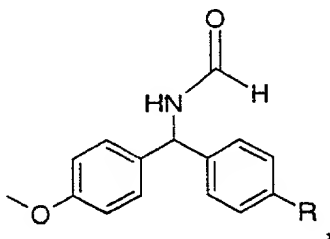
R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

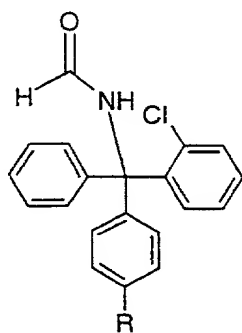
R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

n is an integer from 1 to 4.

25

Preferred intermediates of the present invention are the following compounds;





wherein, R represents the polymeric support either directly attached to the linker or through a spacer moiety, such as a PEG-chain or a $-(CH_2)_n-CONH-$ group.

5

EXAMPLES

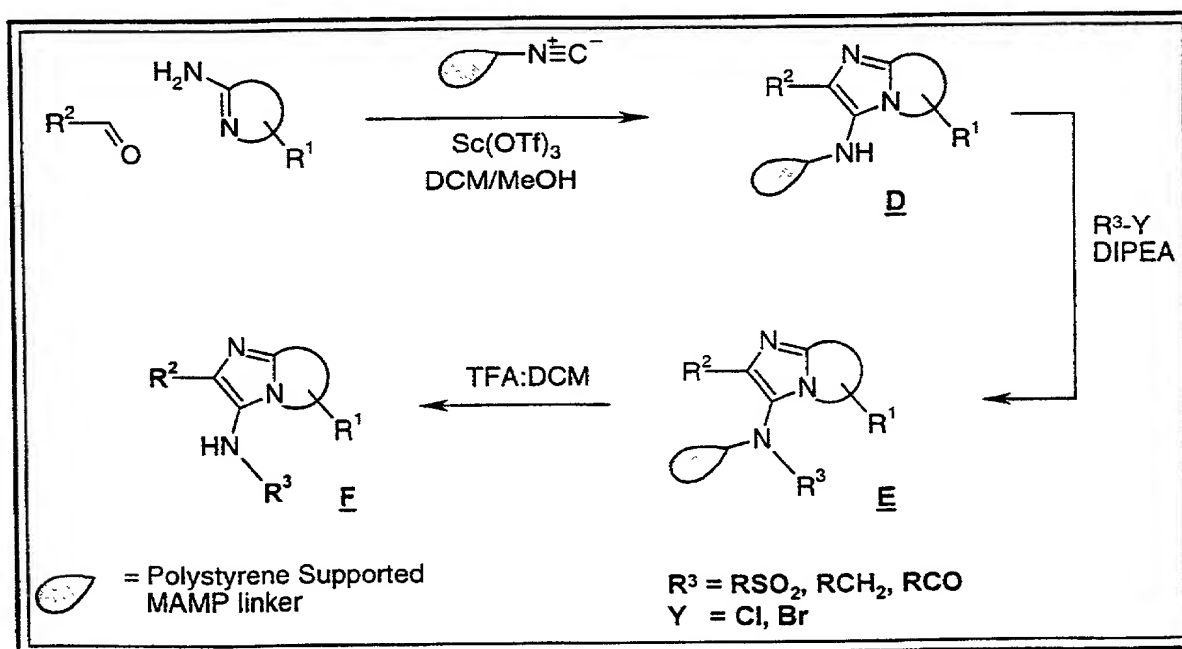
Example 1. Preparation of Functionalized Polymeric Reagent

- 10 The starting MAMP amino resin (1 gr; 1.64mmol/g) was pre-swollen in DMF for 10 minutes. To this resin was added a solution of 2,4,5-trichlorophenyl formate (560mg; 2.46mmol, 1.5eq) in 10 mL of DMF. The reaction mixture was agitated at room temperature for 12h. The resin was filtered and washed with DMF (2x10mL), DCM (2x10mL), MeOH (2x10mL) and finally dry under vacuum for 1 hour. The resin gives a
- 15 negative chloranil test, which indicates completion of the reaction. The resin (1.64mmol) was thereafter washed with dry dichloromethane (2x10mL), pre-swollen in dry dichloromethane for 10 min, and filtered. A solution of triphenylphosphine (2.16g, 8.2mmol, 5eq), carbon tetrachloride (1.27g, 8.2mmol, 5eq) and triethylamine (830mg, 8.2mmol, 5eq) in dry dichloromethane 10mL was added followed by a few activated
- 20 molecular sieves (4Å). The reaction mixture was shaken at room temperature for 3 hours. The resin was filtered, and washed with dichloromethane (2x10mL), methanol (2x10mL), and dichloromethane was added to afford the separation of the floating resin from the molecular sieves. The resin was washed with 10mL dichloromethane and diethyl ether

(2x10mL) and dried under vacuum for 12h. The resin was then kept under nitrogen at room temperature in the dark for 6 months without any modification of its efficiency.

Example 2. Resin Capture Strategy for the synthesis of fused 3-amino imidazoles.

The heteroaromatic amidine (323 μ mol, 200mol%), the aldehyde (323 μ mol, 200mol%) and the catalyst $\text{Sc}(\text{OTf})_3$ (16.2 μ mol, 10mol%) in 1mL of a solution of DCM:MeOH (3:1) were incubated for 30min. The resin isonitrile linker (100mg, 163 μ mol, 100mol%) was preswollen for 20 minutes in DCM and the resin filtered. The solution of aldehyde, heteroaromatic amidines and catalyst was then added to the resin and the solution was shaken for 2 days at room temperature. The resin filtered and washed with DCM(2x3mL), MeOH(2x3mL), 20%DIPEA in DCM(3mL) and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution DCM:4M HCl in dioxane(1:1) for 1h at room temperature. The residue was dried under vacuo and analysed by LC-MS, yielding the expected product in high purity (75-99%).



Scheme 1. Enhancement of diversity by reacting the nitrogen atom, involved in an amine bond with the polymeric support, of the fused 3-aminoimidazole with various electrophiles.

Example 3. Synthesis of amide substituted fused 3-aminoimidazoles

5 Resin-bound compound **D** (60mg, 74 μ mol, 100mol%) was preswollen in DCM for 20 minutes and the resin filtered. A solution of acyl chloride (370 μ mol, 500mol%) and DIPEA (600 μ mol, 800mol%) in 1mL of DCM was added to the resin-bound compound **D** and the reaction mixture was agitated for 20h at room temperature. The resin was filtered and
10 washed with DCM (2x3mL), MeOH (2x3mL), and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution of DCM:TFA:water (80:18:2) for 1h at room temperature. The residue was dried under vacuo and analysed by LC-MS, yielding the expected product in high purity (75-99%).

15 Example 4. Synthesis of alkylated 3-aminoimidazoles.

Resin-bound compound **D** (60mg, 74 μ mol, 100mol%) was preswollen in DMF for 20 minutes and the resin filtered. A solution of alkyl halides (370 μ mol, 500mol%) and DIPEA (740 μ mol, 1000mol%) in 1.2mL of DMF was added to the resin-bound compound **D** and
20 the reaction mixture was agitated for 20h at 80°C. The resin was filtered and washed with DMF (2x3mL), DCM (2x3mL), MeOH (2x3mL), and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution of DCM:TFA:water (80:18:2) for 1h at room temperature. The residue was dried under vacuo and analysed by LC-MS, yielding the expected product in high purity (75-99%).

25 Example 5. Synthesis of sulfonamide substituted 3-aminoimidazoles.

Resin-bound compound **D** (60mg, 74 μ mol, 100mol%) was preswollen in DCM for 20 minutes and the resin filtered. A solution of sulfonyl chlorides (370 μ mol, 500mol%) and
30 DIPEA (740 μ mol, 1000mol%) in 1.2mL of DCM:Dioxane (1:1) was added to the resin-

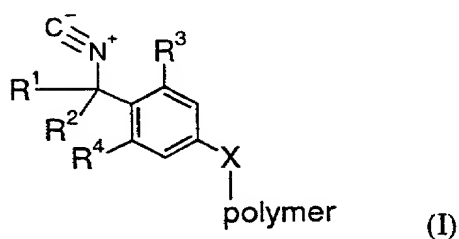
bound compound D and the reaction mixture was agitated for 20h at 60°C. The resin was filtered and washed with DCM (2x3mL), Dioxane (2x3mL), MeOH (2x3mL), and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution of DCM:TFA:water (80:18:2) for 1h at room temperature. The residue was dried under
5 vacuo and analysed by LC-MS, yielding the expected product in high purity.

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CLAIMS

1. A functionalized polymeric reagent for solution and solid-phase synthesis comprising a
 5 polymer and a linker moiety characterized in that the linker comprises an acid labile
 isonitrile moiety.

2. A functionalized polymeric reagent for solution and solid-phase synthesis of Formula I



wherein

X is carbon, oxygen, a PEG-chain, or a $-(CH_2)_n-CONH-$ group,

R^1 is hydrogen, phenyl, or substituted phenyl group,

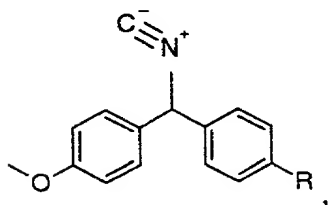
R^2 is hydrogen, phenyl, or substituted phenyl group,

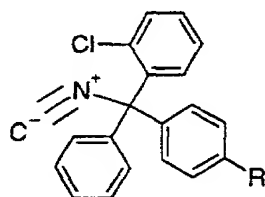
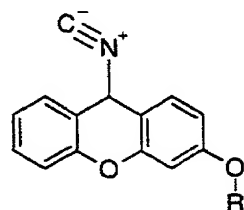
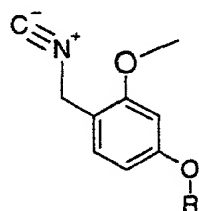
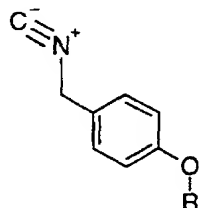
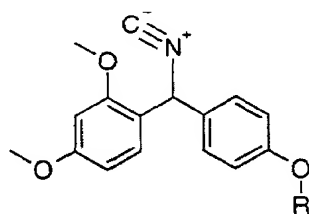
R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

n is an integer from 1 to 4.

3. The functionalized polymeric reagent according to claims 1 or 2 being,





5

wherein R is a polymer directly attached to the linker or through a $-(CH_2)_n-CONH-$ group, or a PEG-chain.

10

4. The functionalized polymeric reagent according to any of claims 1-3, characterized in that the polymer is a soluble polymer.
5. The functionalized polymeric reagent according to any of claims 1-3, characterized in that the polymer is an insoluble polymer.

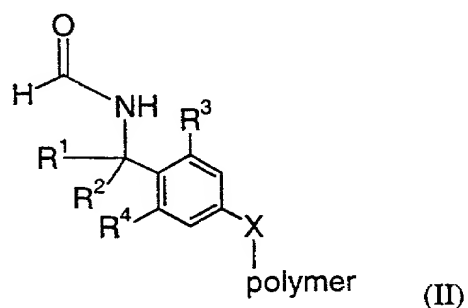
6. A method for preparing a functionalized polymeric reagent according to claims 1-5, comprising the step of.
- a) reacting the polymeric support with a formylating reagent;
 - b) converting the thereby formed formamido group into an isonitrile moiety.
- 5
7. The method according to claim 6, characterized in that the formylating reagent used in step a) is 2,4,5-trichlorophenyl formate.
8. The method according to claim 6 and 7, characterized in that the reagent used in step b) is carbon tetrachloride / triphenylphosphine in the presence of triethylamine.
- 10
9. A method for preparing an organic compound by solution and solid-phase synthesis comprising the steps of
- a) immobilizing a substrate compound to the isonitrile moiety of the functionalized polymeric reagent according to claims 1-4
 - b) performing at least one further reaction step, and
 - c) cleaving the compound from the polymeric support by acid treatment.
- 15
10. The method according to claim 9 comprising an additional reaction step after the cleavage from the polymeric support.
- 20
11. The method according to claim 9, characterized in that the method is performed with a plurality of substrate compounds and/or plurality of further reaction steps to give a library of organic compounds.
- 25
12. The method according to claim 9, characterized in that at least one of the reaction steps is a multicomponent reaction.

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13. A kit comprising a container of a functionalized polymeric reagent according to claims

1-4.

14. Intermediate compounds of Formula II



wherein

X is carbon, oxygen, a PEG-chain, or a $-(CH_2)_n-CONH-$ group,

R^1 is hydrogen, phenyl, or substituted phenyl group,

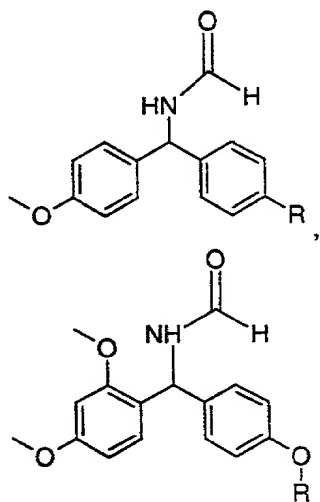
R^2 is hydrogen, phenyl, or substituted phenyl group,

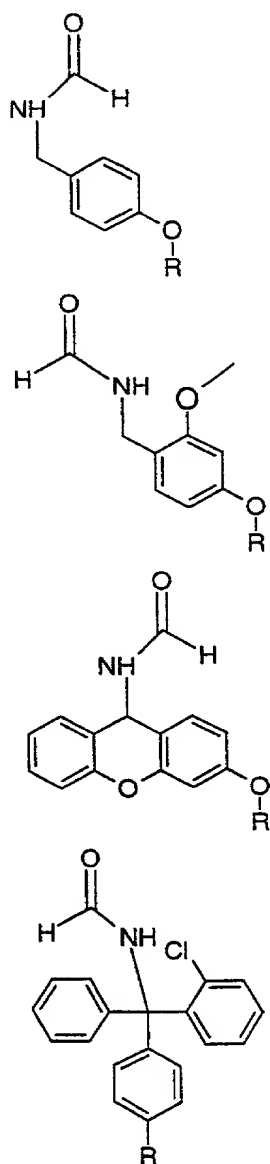
R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

n is an integer from 1 to 4.

15. Compounds according to claim 13 being





- 5 wherein, R represents the polymeric support either directly attached to the linker or through a spacer moiety, such as a PEG-chain or a $-(CH_2)_n-CONH-$ group.

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled NEW FUNCTIONALIZED POLYMERIC REAGENTS the specification of which is attached hereto unless the following box is checked:

☒ was filed on 16 November 2000 as United States Application Number or PCT International Application Number PCT/SE00/02263 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

9904222-8
(Number)

Sweden
(Country)

22 November 1999
(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

(Application Number)

(Filing Date)

(Application Number)

(Filing Date)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application Number)

(Filing Date)

(Status -- patented, pending, abandoned)

(Application Number)

(Filing Date)

(Status -- patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Nels T. Lippert, Reg. No. 25,888; Dimitrios Drivas, Reg. No. 32,218; Robert B. Smith, Reg. No. 28,538; David Bender, Reg. No. 35,445; John M. Genova, Reg. No. 32,224; Richard J. Sterner, Reg. No. 35,372; Hans-Peter G. Hoffmann, Reg. No. 37,352; Cecilia O'Brien Lofters, Reg. No. 33,434; Leslie Morioka, Reg. No. 40,304; John Scheibeler, Reg. No. 35,346; Thelma A. Chen Cleland, Reg. No. 40,948; Jean E. Shimotake, Reg. No. 36,273; Jeff Oelke, Reg. No. 37,409; Thomas E. Malone, Reg. No. 40,078; and Douglas R. Nemec, Reg. No. 41,219, all of the firm of WHITE & CASE Limited Liability Partnership, with offices at 1155 Avenue of the Americas, New York, New York 10036.

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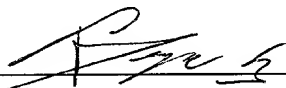
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Full name of sole or first inventor
(given name, family name)

Patrick Page

First inventor's signature



Date:

20th December 2000

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